

923-67 Bronchial Hyperresponsiveness (BHR) in Congestive Heart Failure (CHF) May Be Mediated by Impairment of the Pulmonary Adrenergic Signal Transduction Pathway

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Wheezing often aggravates the clinical symptoms of CHF. Part of this BHR may be mediated by vascular congestion and vagal reflexes. Changes of the adrenergic signal transduction pathway in the lung may add to the clinical symptoms, but they have not been investigated so far. To clarify whether an impairment of β -adrenergic signal transduction pathway might contribute to BHR in CHF, the adrenergic signal transduction system was studied in rats 4 weeks after aortic banding. At that time, LVEDP (11 ± 1 vs. 5 ± 1 mmHg), lung wet weight (1968 ± 199 vs. 1216 ± 74 mg), and plasma norepinephrine levels (0.56 ± 0.10 vs. 0.34 ± 0.06 nM) had increased significantly. Beta-adrenergic receptor densities (β AR) and affinities (K_D) were determined in pulmonary plasma membrane preparations by radioligand binding assays using [125 I]iodocyanopindolol. Compared to sham-operated controls ($n = 8$), β AR were decreased in CHF ($n = 9$) to 585 ± 44 vs. 791 ± 101 fmol/mg protein ($p < 0.05$). The densities of β AR were negatively related to lung wet weight ($r = -0.71$, $p < 0.05$). K_D values remained unchanged (25 ± 3 vs. 20 ± 3 pM). Receptor-independent, sodium-fluoride stimulated adenylyl cyclase activity in lung membranes was decreased by 28% ($p < 0.05$) in CHF. On a functional level, the isoproterenol-induced relaxation of isolated tracheal rings precontracted with carbachol was also significantly blunted when compared to controls.

Conclusions: These data demonstrate for the first time that neuroendocrine activation in CHF is associated with a downregulation of pulmonary β -adrenergic receptors and of pulmonary adenylyl cyclase activity, leading to an impaired response of airway smooth muscle to adrenergic stimuli. Thus, BHR in CHF may be in part due to a reduction in β -adrenergic bronchodilatory tone and contribute to the clinical manifestation of "cardiac asthma".

923-68 Chronically Infarcted Hearts Exhibit Increased Susceptibility to High-Workload — but Not to Low-Workload — Metabolic Stress

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In residual intact myocardium of chronically infarcted hearts, energy reserve via creatine kinase is reduced: Total creatine kinase, total creatine and creatine kinase reaction velocity are all reduced by up to 50%. For hearts of transgenic mice with a null-mutation of the creatine kinase-M gene, susceptibility to ischemia/reperfusion is unchanged, but susceptibility to high-dose isoproterenol is increased. We tested whether this is also true for failing chronically infarcted hearts. Two months following infarction (MI) or sham operation, rat hearts were isolated and buffer-perfused isovolumically with end-diastolic pressure set to values measured before *in vivo*. 31 P-NMR spectra were obtained in 5 min intervals at 7 Tesla. In protocol 1, hearts (sham: $n = 10$, MI: $n = 5$) were subjected to 15 min of total global ischemia followed by reperfusion. During ischemia and reperfusion, changes of ATP (end of ischemia: 3.7 ± 0.3 mM in sham, 3.8 ± 0.4 mM in MI hearts), phosphocreatine (Reperfusion: 11.3 ± 0.8 mM in sham and 11.4 ± 1.4 mM in MI hearts) and mechanical performance were similar. In protocol 2, sham ($n = 10$) and MI hearts ($n = 6$) were subjected to isoproterenol-infusion at increasing dosages (10, 100, 250 ng/min). Here, increases of rate-pressure products were similar for sham and MI; however, during inotropic stimulation, phosphocreatine depletion was greater in infarcted hearts (PCR: $64 \pm 3\%$ of control at 250 ng/min) than in sham (PCR: $79 \pm 2\%$; $p < 0.005$). Conclusion: Similar to creatine kinase-M-deficient hearts, chronically infarcted hearts with reduced energy reserve via creatine kinase show unaltered susceptibility to metabolic stress associated with low workload (ischemia/reperfusion), but increased susceptibility to metabolic stress associated with high workload (isoproterenol stimulation).

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Presentation Hour: 3:00 p.m.—4:00 p.m.

924-69 The Relationships Between Endothelin-1 Secreted During Exercise and Pulmonary Vascular Tone in Patients With Mild Mitral Stenosis

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The purpose of this study is to clarify the relationships between plasma endothelin-1 (ET) secreted during exercise and the hemodynamic parameters in patients with mild mitral stenosis (MS).

We measured respiratory variables and determined the anaerobic threshold (AT) during ramp loading cycle ergometer of 15 patients with MS (MVA = 1.56 ± 0.51 cm², Pulmonary artery pressure (PPA)-systolic = 35.1 ± 8.3 mmHg) and 4 normal subjects (control). Arterial blood samples were obtained at rest (ET-rest) and 3 minutes after AT was recognized (ET-AT), and plasma concentrations of ET were measured using sandwich-type enzyme immunoassay. Hemodynamic parameters were obtained by cardiac catheterization. **Results:** 1) Both ET-rest and ET-AT in MS (1.11 ± 0.74 , 1.30 ± 0.77 pg/ml) were significantly higher than in the control (0.62 ± 0.12 , 0.66 ± 0.12 , $p < 0.05$, respectively). 2) ET-AT were significantly increased than ET-rest in MS ($p < 0.05$). 3) The correlations between ET-rest, ET-AT or d-ET (ET difference between at rest and AT) and hemodynamic parameters in MS were as follows:

	ET-rest	ET-AT	d-ET
PPA-systolic	NS	$r = 0.57$ $p < 0.05$	$r = 0.55$ $p < 0.05$
PPA-mean	NS	$r = 0.58$ $p < 0.05$	$r = 0.59$ $p < 0.05$
TPRI	$r = 0.82$ $p < 0.001$	$r = 0.87$ $p < 0.001$	NS

Conclusion: These data suggest that not only an increase of ET at rest but also ET secreted during exercise at the AT level is implicated to increase of pulmonary vascular tone in patients with MS.

924-70 Absence of Functional Mitral Regurgitation (MR) Despite Severely Reduced Left Ventricular Function: Insights Into the Mechanism of MR

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Recent studies have suggested that global LV systolic dysfunction primarily determines functional MR. Clinical observations, however, suggest there are patients with severely reduced global function but no MR. We explored this observation by reviewing 1,366 consecutive patients studied by 2D echo and color Doppler with LV ejection fractions (EFs) $< 30\%$ (mean, $17.8 \pm 6\%$), of whom 190 (14%) had no MR. We then randomly selected 34 patients, 17 with and 17 without MR, for quantitative analysis, including: LV EF by biplane Simpson's, LV internal diameters and sphericity ratio of short-to-long-axis diameters; mitral annular size; MR jet area and proximal width; and the incomplete mitral leaflet closure (IMLC, tenting) area apical to the annulus (4-chamber). **Results:** LVEF was not significantly different between those without and with MR (17.8 ± 5.9 vs $17.7 \pm 6.0\%$), as was age. Patients without MR had: 1) smaller LVs in systole (58 ± 9 vs 66 ± 8 mm, $p < 0.02$) and diastole (63 ± 10 vs 72 ± 6 mm, $p < 0.005$); 2) 24% vs 81% of pts without MR had systolic diameters > 60 mm ($p < 0.002$), and several had pericardial limitation; 3) lower LV sphericity in systole and diastole ($p < 0.007$); 4) smaller mitral annuli (40 ± 6 vs 45 ± 5 mm, $p < 0.03$); and 5) smaller IMLC areas (1.1 ± 0.5 vs 3.1 ± 1.4 cm², $p < 0.006$). Multiple linear regression showed that MR presence and amount correlated with both IMLC and LV sphericity ($r^2 = 0.64$), and the IMLC area correlated best with sphericity ($r^2 = 0.27$). **Conclusions:** MR may be absent despite severely reduced LV systolic function. Changes in LV size and shape correlate with functional MR, which is related to apical leaflet tenting, consistent with abnormal tethering by displaced attachments.

924-71 Effect of Acute Beta-Adrenergic Blockade on the Severity of Mitral Regurgitation in Chronic Canine Mitral Regurgitation

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Acutely, β -blockers precipitate decompensation in chronic mitral regurgitation

(MR). This occurs, in part, by unmasking contractile dysfunction. Since MR may be dynamic and vary with contractile state, decompensation may also be due to worsening MR. This study tested the hypothesis that acute β -blockers increase the severity of MR.

Ten dogs with severe MR were instrumented with ultrasonic crystals to measure LV volume. LV pressure measurements allowed for assessment of contractile function. Forward stroke volume (FSV) was measured using the thermodilution technique. Regurgitant fraction (RF) and regurgitant volume (RV) were calculated as the difference between the volumetric stroke volume and the FSV. In a second group of six dogs, regurgitant orifice area (ROA) was measured using echocardiography. Measurements were done under control conditions (C); during esmolol infusion 300 mcg/kg/min (E); and during dobutamine infusion 30 mcg/kg/min (DB).

	LAP	FSV	RF	RV	dP/dt	ROA
C	11 \pm 7	31 \pm 8	54 \pm 12	40 \pm 19	2402 \pm 606	0.60 \pm 24
E	21 \pm 9*	17 \pm 7*	69 \pm 16*	49 \pm 24	1636 \pm 517*	0.73 \pm 20
DB	5 \pm 5*	40 \pm 8	40 \pm 15*	41 \pm 28	4302 \pm 1137*	

*significantly different from C: $p < 0.05$; LAP = left atrial pressure

Acute β -blockade precipitates hemodynamic decompensation by decreasing FSV and contractility; however, the severity of MR, as assessed by RV and ROA, is unchanged.

924-72 The Significance of an Audible S3 is Different in Aortic Regurgitation, Mitral Regurgitation and LV Dysfunction: A Quantitative Doppler Echocardiographic Study

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An audible S3 is frequently heard in pts with aortic (AR) or mitral (MR) regurgitation or LV dysfunction (LVD), but its significance has not been fully clarified. In 340 pts (mean age 64 \pm 14), an S3 noted by an independent clinician was correlated to noninvasive echocardiographic LV volumes at end diastole (EDVI) and end systole (ESVI), ejection fraction (EF), mitral E wave and deceleration time (DT), and regurgitant fraction (RF) measured by two methods (quantitative Doppler and 2D echocardiography). An S3 was noted in 9/61 pts (15%) with AR, 28/176 pts (16%) with MR, and 46/103 pts (45%) with LVD ($p < 0.0001$). Baseline characteristics in pts with and without an S3 were:

S3	AR		MR		LVD	
	Yes	No	Yes	No	Yes	No
EDVI (ml/m ²)	143	107 [†]	136	101*	149	138
ESVI (ml/m ²)	67	40*	30	35*	97	108
EF (%)	53	63*	62	65	29	32
RF (%)	42	36	92	55*	30	23 [†]
DT (ms)	202	231	187	204	142	184*

* $p < 0.001$, [†] $p < 0.01$

In multivariate analysis the independent predictors for an S3 were different: ESVI ($p = 0.0001$) for AR, RF ($p = 0.007$) in association with EDVI ($p = 0.0001$) or ESVI ($p = 0.03$) depending on the model used for MR, and shortened DT ($p = 0.0001$) for LVD. The positive and negative predictive values of an S3 were 56% and 85% for ESVI ≥ 60 ml/m² in AR, 71% and 67% for RF $\geq 50\%$ in MR and 74% and 58% for restrictive LV filling in LVD. We conclude that an audible S3 1) has a different frequency and meaning in various heart diseases, 2) is associated with decreased LV function and enlarged ESVI in AR, 3) severe regurgitation and LV enlargement in MR, 4) restrictive LV filling in LVD. This data should allow improved pathophysiologic bedside interpretation of the physical examination.

924-73 HLA-DR/DQ Associations With Rheumatic Heart Disease (RHD) in Mexicans

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There is increasing evidence to indicate that RHD may be genetically programmed to respond abnormally to streptococcal infections and HLA antigens seem to play a central role. We included 107 Mexican patients diagnosed as RHD according to the revised Jones Criteria. Of the total, 67.6% were females and 25% were non-adults; 6.3% had family history of rheumatic fever. The majority were born in the highlands of Mexico (77%). A group of 229 healthy controls was included for comparison. All subjects are Mexican Mestizos. Venous blood samples were withdrawn and HLA typing for class I (A,B,C) and class II (DR, DQ) antigens was performed on T and B cells respectively, isolated from mononuclear cells. The standard microcytotoxicity

method was used for typing. No deviation for class I antigens was observed. DR17 was found increased in the patients ($p = 0.002$). The p = NS, the RR = 2.73 and the χ^2 = 0.14. The supertypic DR53 showed an intense association ($p = 0.02$) with a similar RR = 2.54, but an EF = 0.45, suggesting that the true susceptibility genes are located in an epitope of this molecule. A resistance gene is also present; DQ6 was significantly decreased ($P = < 0.0003$) with a strong PF = 0.37. All possible correlations between the class II molecules and the clinical parameters were analyzed to determine if an HLA marker can be responsible for severity. Even if 53.3% of the cases had carditis, 42.2% suffered from polyarthritis and 64.8% had affected the mitral valve (12.1% were aortic and 23.1% were mitro-aortic), no class II antigen predisposes to any manifestation or to subgroups of age-at onset. In conclusion, DR53 is an important marker for susceptibility and DQ6 is a strong protective factor. DNA typing is now under way to localize the exact sequences involved in the expression of RHD.

924-74 Detection of Thoracic Aortic Plaque (AP) by Multiplane Transesophageal Echocardiography (TEE) Can Predict Coronary Artery Disease (CAD) in Valvular Heart Disease (VHD). A Large Prospective Study

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The purpose of this prospective study using a multiplane probe was to examine whether TEE absence or detection of AP could predict CAD in 221 consecutive VHD pts with VAD aged ≤ 70 years. In 70 pts with significant CAD, 66 had AP. AP existed in only 21 of the 151 pts with normal or subnormal coronary arteries. In the 221 pts, the presence of AP on TEE study had a sensitivity of 91%, a specificity of 86%, a positive and negative predictive values of 75% and 96% for significant CAD. In 86 patients aged ≥ 70 years, these sensitivity, specificity, and positive and negative predictive values were 97%, 79%, 79%, and 97% respectively. There was a close relation between the degree of aortic intimal changes and the severity of CAD ($p < 0.00001$). Multivariate stepwise regression analysis of pt age, sex, risk factors of CAD, angina and TEE findings revealed that AP, angina, hypercholesterolemia were significant independent predictors of CAD. AP was the most significant independent predictor even in pts aged ≥ 70 years.

This prospective study indicates that AP on TEE is a powerful predictor of the absence or presence and severity of CAD in VHD, even in pts aged ≥ 70 years.

924-75 How Reliable Is Transesophageal Echocardiographically-Detected Aortic Atherosclerosis to Predict Coronary Artery Disease in Patients With Valvular Heart Disease?

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Vascular atherosclerosis is a general process that may involve the coronary arteries as well as the peripheral arteries including the aorta. To determine whether coronary artery disease (CAD) (defined as the presence of any atherosclerotic plaque on coronary angiography) could be predicted by transesophageal echocardiographically (TEE)-detected aortic atherosclerosis, we retrospectively reviewed data from 100 consecutive pts who had undergone both TEE and coronary angiography within a 30-day period of time. The clinical indication for coronary angiography was the presence of valvular heart disease likely to require surgical treatment. The patients were 59 men and 41 women with a mean age of 60 \pm 11 years. The thoracic aorta was considered normal when the intimal surface was smooth and continuous without lumen irregularities, and atherosclerotic when changes were observed, consisting of increased echodensity of the intima with or without lumen irregularities, ulceration or protruding thrombus.

Aortic atherosclerosis was observed on TEE in 50 pts. Any CAD was present on coronary angiography in 52 pts (52%) (gr1), among whom 15 had obstructive CAD ($> 50\%$ diameter stenosis) (gr2). The sensitivity (Se)(%), specificity (Sp)(%), positive predictive value (PPV)(%) and negative predictive value (NPV)(%) of TEE-detected aortic atherosclerosis for the presence of CAD were determined for both groups:

	Se	Sp	PPV	NPV
Gr1	86	89	90	86
Gr2	86	56	26	96

TEE-detected aortic atherosclerosis is a reliable marker for the presence of any CAD. However, though the NPV is excellent for the presence of obstructive CAD, it is insufficient to accurately predict the severity of CAD in valvular heart disease pts.